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(71) Applicant *(for all designated States except US)*: RICHTER GEDEON VEGYÉSZETI GYÁR RT. [HU/HU]; Gyömrői út 19-21, H-1475 Budapest (HU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : DOMÁNY, György [HU/HU]; Bimbó u. 114/a, H-1022 Budapest (HU). BARTÁNÉ, Szalai, Gizella [HU/HU]; Agyagfejtő u. 4, H-1108 Budapest (HU). SCHÖN, István [HU/HU]; Ráskai Lea u. 86, H-1142 Budapest (HU). HEGEDÜS, Béla [HU/HU]; Bartók Béla u. 82, H-1113 Budapest (HU). TRISCHLER, Ferenc [HU/HU]; Uttörő u. 16, H-1171 Budapest (HU). SZPORNY, László [HU/HU]; Szabolcska M. u. 7, H-1114 Budapest (HU). KISS, Béla [HU/HU]; Gergely u. 48, H-1103 Budapest (HU). KÁRPÁTI, Egon [HU/HU]; Mihályfi Ernő u. 7/b, H-1022 Budapest (HU). PÁLOSI, Éva [HU/HU]; Vend u. 21, H-1025 Budapest (HU). SARKADI, Ádám [HU/HU]; Thököly u. 85, H-1146 Budapest (HU). GERE, Anikó [HU/HU]; Egry J. u. 40, H-1111 Budapest (HU). CSOMOR, Katalin [HU/HU]; Nyár u. 99, H-1045 Budapest (HU). LASZY, Judit [HU/HU]; Beregszász u. 40, H-1112 Budapest (HU). SZENTIRMAI, Zsolt [HU/HU]; Mosolygó A. u. 26/a, H-1158 Budapest (HU). LAPIS, Erzsébet [HU/HU]; Abaliget u. 86, H-1172 Budapest (HU). SZABÓ, Sándor [HU/HU]; Liszt Ferenc tér 9, H-1061 Budapest (HU). THURÓCZYNÉ, Kálmán, Eszter [HU/HU]; Törökugrató út 5, H-1118 Budapest (HU). CSEHI, Attila [HU/HU]; Lánchid u. 15, H-2131 Göd (HU).

(74) Agent: DANUBIA; Bajcsy Zsilinszky út 16, H-1051 Budapest (HU).

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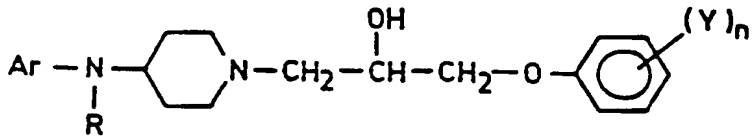

(I)

(57) Abstract

The invention relates to novel optically active and racemic aminopropanol derivatives of formula (I) wherein R means hydrogen or a C_{1-4}alkyl group; Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group; Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and n is an integer of 0, 1, 2, 3, 4, or 5 as well as acid addition salt of these compounds. The invention further relates to pharmaceutical compositions containing these compounds as well as a process for the preparation of the compounds of formula (I). The compounds of formula (I) are useful for inhibiting the peroxidation of lipids and treating the sequels thereof as well as for protection from or treatment of the sequels of calcium-mediated injuries induced e.g. by ischemia, hypoxia or reperfusion and for treating various degenerative neurological diseases e.g. Alzheimer's disease or Parkinson's disease.

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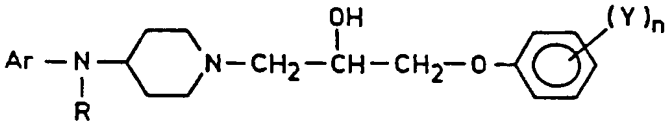
NOVEL AMINOPROPANOL DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME

The invention relates to novel, therapeutically active aminopropanol derivatives of formula



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

n is an integer of 0, 1, 2, 3, 4 or 5

in racemic or optically active form as well as their acid addition salts and pharmaceutical compositions containing these compounds. Furthermore, the invention relates to a process for the preparation of the above compounds and compositions.

The compounds of formula (I) according to the invention are new and possess a valuable biological activity. Under in vitro conditions they show a significant anti-oxidant (lipid peroxidation inhibitory) and neuronal Ca

uptake inhibitory effect. By investigating under in vivo conditions, they exert a remarkable antihypoxic and anti-convulsive action.

Accordingly, the invention relates also to a method of treatment, which comprises administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof to a patent for inhibiting the lipid peroxidation and for protection from or treatment of Ca-mediated injuries and the sequels thereof.

In the formula (I) the C_{1-4}alkyl group or C_{1-4}alkyl moiety of the C_{1-4}alkoxy group may be a straight or branched chain alkyl group. The term halogen includes e.g. fluorine, chlorine or bromine.

There are compounds known from the literature, which are structurally related to the compounds of the formula (I).

Antihypoxically active substances, which are similar to the compounds of the present invention but bear a heterocyclic (benzoxazole, benzothiazole) substituent on the amino group of the 4-aminopiperidine moiety, are described in the European patent specification No. 184,257.

Analgetically active 4-arylaminopiperidine derivatives substituted by a 4-arylbutyl or a 3-aroylpropyl group and a 3-arylpropyl group, respectively on the nitrogen of the piperidine ring are described in US patent specifications Nos 3,686,187 and 3,691,171.

Analgetically active 4-(1-naphthylamino)piperidine derivatives substituted by a 2-arylethyl substituent in position 1 of the piperidine ring are disclosed in the Swiss patent specification Nos. 528,507 and 535,767.

Due to hypoxia, ischemia (global or focal, permanent or transient) or reperfusion, the cognitive functions are damaged [S. N. Weinachter et al.: Group

Report 8: "Models of Hypoxia and Cerebral Ischemia" Pharmacopsychiat. 23, pages 94 to 98 (1990)].

Depending on the severity and duration of hypoxia and ischemia, reversible or irreversible injuries occur: the structure and function of the membrane are damaged, which may lead to neuronal death.

As a consequence of hypoxia and ischemia, the mitochondrial ATP production ceases and an aerobic glycolysis develops, which results in lactic acid acidosis. Due to the ATP definiciency, the function of ion-pumps is stopped [T. F. Hornbein: "Hypoxia and the Brain" in: R.G. Crystal and J. B. West eds. The Lung: Scientific Foundations, pages 1535 to 1541 (1991)]. The K^+ concentration of the extracellular spaces significantly increases, which leads to membrane depolarization inducing the opening of potential-dependent Ca channels. The influx of Ca to the cell partly proceeds through these Ca channels.

The increase in the Na^+ permeability of the membrane induces the release of a large amount of excitatory amino acids (glutamate, aspartate). Glutamate activates the receptor-dependent Ca channels, through which Ca similarly may penetrate into the cell [B. K. Siesjö et al.: "Calcium Fluxes, Calcium Antagonists and Calcium-Related Pathology in Brain Ischemia, Hypoglycemia, and Spreading Depression: A Unifying Hypothesis. J. Cereb. Blood Flow Metab. 9, pages 127 to 140 (1989)].

The influx of Ca to the cell (pre- and postsynaptic Ca influx) may induce catabolic reactions. The increase in the intracellular Ca may initiate reactions significantly influencing the functions and integrity of the cells.

Ca-induced abnormal reactions include lipolysis, proteolysis, disintegration of the microtubules, high-grade phosphorylation of proteins, release of catecholamines in remarkable amounts and formation of free radicals [B. K. Siesjö et al.: "Brain Injury: Neuro-

chemical Aspects" in: J. Povlishoch and C. Becker eds. Central Nervous System Trauma-Status Report, pages 513 to 532 (1984)].

Blocking of the Na and Ca channels may play an important role in the mode of action of cerebroprotective compounds.

Use of tetrodotoxin blocking the Na channel proved to be favourable in the protection from ischemic injuries [Y. Yamasaki et al.: "The Possible Involvement of Tetrodotoxin-sensitive Ion Channels in Ischemic Neuronal Damage in the Rat Hippocampus" Neurosci. Lett. 121, pages 251 to 254 (1991); as well as D. Ashton et al.: "Extracellular Ions During Veratridine-induced Neurotoxicity in Hippocampal Slices: Neuroprotective Effects of Flunarizine and Tetrodotoxin" Brain Res. 528, pages 212 to 222 (1990)].

Compounds decreasing the pre- and postsynaptic Ca uptake or altering the accumulation of Ca on intracellular sites may be of therapeutical importance. At present, the Ca antagonists are used for treating ischemic injuries mainly on the basis of their vascular effects; however, it seems more and more important that compounds possessing such a mechanism of action exert their antihypoxic and antiischemic effects through inhibition of the Ca influx to neurons [R. Hall et al.: "Brain Protection: Physiological and Pharmacological Considerations" Part II: The Pharmacology of Brain Protection" Can. J. Anaesth. 37, pages 762 to 777 (1990)].

During the reperfusion following ischemia, a large amount of free radicals are formed. Hydroxyl and hyperoxide radicals may arise in the mitochondrial respiratory chain, in the arachidonic acid cascade in the course of functioning of cyclooxygenase and lipoxygenase, because of the activation of xanthine oxidase and as a result of the autooxidation of catecholamines [T. F. Hornbein:

Hypoxia and the Brain" in: R. G. Crystal and J. B. West eds. The Lung: Scientific Foundations, pages 1535 to 1541 (1991)].

Due to their lipid peroxidation inhibitory effect, antioxidant compounds provide protection against injuries induced by free radicals under ischemic, hypoxic conditions. Thus, antioxidants as antiischemic and anti-hypoxic compounds can be used for the treatment of such clinical syndromes [R. J. Traystman et al.: "Oxygen Radical Mechanisms of Brain Injury Following Ischemia and Reperfusion" J. Appl. Physiol. 71, pages 1185 to 1195 (1991)].

Free radical reactions likely play a causal role in the pathogenesis of ischemia-induced injuries such as ischemic intestinal diseases, myocardial ischemia, haemorrhagic shock, cerebrovascular function disturbances accompanied by ischemia, ischemic liver injury and renal ischemia [R. J. Korthuis et al.: "Physiology of Oxygen Radicals" Chapter 17, pages 217 to 249 (1986)].

In vitro tests for investigation of the antioxidant effect

The antioxidant effect was studied by using two methods.

1. **Effect on the NADPH-induced lipid peroxidation in brain microsomes**

This investigation was carried out on microsomes prepared from rat brain by following the method of T. J. Player and A. A. Horton [J. Neurochem. 37, (2), pages 422 to 426 (1981)].

Male Hannover-Wistar rats weighing 150-250 g each were used for the preparation of microsomes. After decapitation the whole brain of the rat was removed and homogenized in a 10-fold volume of ice-cold 0.25 M sucrose solution. The homogenate was centrifuged in a Hitachi CR 26H equipment at 15,000 x g at 4 °C for 10 minutes, then the supernatant was collected and centrifuged

in a Hitachi SCP85H equipment at 78000 x g at 4 °C for 60 minutes. The pellet was suspended in 0.15 M KCl solution, the protein content was determined and then adjusted to 10 mg/ml. The microsome preparation thus obtained was frozen in a dry ice-acetone mixture and stored at -70 °C until use.

The components of the incubation mixture were: 50 mM TRIS.HCl (pH 6.8), 0.2 mM $FeCl_3$, 1 mM KH_2PO_4, 0.5 mM ADP, 0.2 mg of microsomes as well as the compound to be tested. The incubation was carried out in a final volume of 1 ml with an incubation time of 20 minutes at a temperature of 37 °C. The lipid peroxidation was induced by adding 0.4 mM NADPH. (The blank samples did not contain NADPH.) The reaction was stopped by adding 0.375 ml of a stopping solution containing 40% trichloroacetic acid and 5 M HCl in a 2:1 ratio. The formation of malondialdehyde was determined by using thiobarbituric acid. After stopping the reaction 1 ml of 1% thiobarbituric acid was added to the samples, which were then placed in a water bath of about 100 °C for 10 minutes. Subsequently, the samples were centrifuged at 2,000 x g in a Janetzki K70 equipment at 4 °C for 10 minutes. The absorbance values of the coloured supernatant were measured at 535 nm on a Hitachi 150-20 spectrophotometer by using malondialdehyde-bis(diethyl acetal), as a reference compound.

2. Effect on the Fe^{2+}-induced lipid peroxidation in brain homogenate

This investigation was carried out on rat brain homogenate by following the method of J. M. Braughler et al. [J. Biol. Chem. 262 (22), pages 10438 to 10440 (1987)].

After decapitating Hannover-Wistar rats weighing 150-220 g each, the whole brain was homogenized in 9 volumes of ice-cold Krebs-Ringer's buffer (containing 15 mM HEPES (pH 7.4), 140 mM NaCl, 3.6 mM KCl, 1.5 mM

$CaCl_2$, 0.7 mM $MgCl_2$, 1.4 mM KH_2PO_4 and 10 mM glucose). Then the protein content of the solution was determined and adjusted to 10 mg/ml. After adding the inhibitory agent to be tested in a volume of 5 µl to 200 µl of the homogenate, the mixture was incubated at 37 °C for 20 minutes. The Fe^{2+}-induced lipid peroxidation was accomplished by adding 5 µl of a 8 mM $Fe(NH_4)_2(SO_4)_2$ solution. After passing of the incubation time, the reaction was stopped by adding 1 ml of a stopping solution containing 0.8 M HCl and 12.5% of trichloroacetic acid, then the samples were centrifuged at 2,000 x g in a Janetzki K70 equipment at 4 °C for 10 minutes.

To a 0.5 ml portion of the supernatant 1 ml of an 1% thiobarbituric acid solution was added, then the samples were placed in a water bath of 100 °C for 20 minutes. The colour intensity developed was determined at 535 nm with the aid of a Hitachi 150-20 spectrophotometer by using malondialdehyde-bis(diethyl acetal), as a reference compound.

On the basis of the concentration/effect correlations of the tested compounds the IC_{50} values were determined; these results are indicated in Table I.

Table I

Compound No.	Example No.	Inhibition of the NADPH-induced lipid peroxidation IC_{50} (μM)	Inhibition of the Fe^{2+}-induced lipid peroxidation IC_{50} (μM)
0107966	1	2.1	7.7
0107968	2	1.8	9.5
0108199	1	1.6	1.2
0108487	2	7.0	57.1
0108534	3	0.5	1.6
0108535	3	0.5	1.6
0108536	2	0.8	1.5
0108651	3	2.4	4.7
0108858	1	0.7	7.8
0108859	1	3.1	37.9
0109001	2	1.7	5.7
0109222	1	2.4	2.5
0109223	2	0.7	2.5
Idebenone		1.2	12.5
DL-α-Tocopherol		N.I.	10.5
Ellagic acid		39.2	51.0
Silymarin		197.0	33.2

N.I.: The reaction investigated is not inhibited by the compound

It can be seen from the data of Table I that each of the compounds prepared in the various Examples exerted an antioxidant (lipid peroxidation inhibitory) activity. The antioxidant effect was investigated both in an enzymatic (NADPH-induced) and a non-enzymatic (Fe^{2+}-induced) lipid peroxidation test.

The level of the antioxidant activity of the compounds was characterized by their IC_{50} values. The cerebroprotective idebenone, the native antioxidant vitamin E (DL-α-tocopherol), the anticarcinogenic ellagic acid and the hepatoprotective silymarin were used, as reference compounds.

Based on the data of Table I, the tested compounds showed a much higher activity in the inhibition of the NADPH-induced (enzymatic) lipid peroxidation than the reference compounds (DL-α-tocopherol, ellagic acid, silymarin). The antioxidant effect of the compounds Nos. 0107966, 0107968, 0108199 and 0109001 was comparable to that of idebenone; whereas the compounds Nos. 0108534, 0108535, 0108536, 0108858 and 0109223 exerted a stronger inhibitory effect on the NADPH-induced lipid peroxidation than that of idebenone.

Each of the compounds listed in Table I showed a much stronger inhibitory effect on the Fe^{2+}-induced (non-enzymatic) lipid peroxidation than the reference compounds. Compounds Nos. 0108199, 0108534, 0108535 and 0108536 proved to be particularly active since each of them was ten times as active as idebenone or DL-α-tocopherol. Similarly, the compounds Nos. 0109222, 0109223, 0108651 and 0109001 inhibited the Fe^{2+}-induced lipid peroxidation considerably. The antioxidant activity of the compounds Nos. 0107966, 0107968 and 0108858 also exceeded that of the reference compounds.

By comparing the data in the in vitro antioxidant tests it can be stated that the substances Nos. 0109223, 0108534, 0108535, 0108536 and 0108858 exerted a higher inhibitory effect on the lipid peroxidation induced in various ways, than idebenone, found to be the most active reference compound up to the present.

The compounds according to the invention possess a significant antioxidant effect namely, they are capable to

inhibit the lipid peroxidation processes induced by free radicals arising from Fenton's reaction (catalyzed by Fe^{2+}) or during the functioning of the NADPH-cytochrom C reductase enzyme.

Abbreviations:

NADPH: β-Nicotinamide adenine dinucleotide phospate, reduced form

TRIS: Tris(hydroxymethyl)aminomethane

ADP: Adenosine-5'-diphospate

HEPES: 2-[4-(2-Hydroxyethyl)-1-piperazine]-ethane-sulfonic acid

Idebenone: 6-(10-Hydroxydecyl)-2,3-dimethoxy-5-methyl--1,4-benzoquinone

DL-α-Tocopherol: [2,5,7,8-Tetramethyl-2-(4',8',12'-trimethyl-tridecyl)-chroman-6-ol

Ellagic acid: 2,3,7,8-Tetrahydroxy[1]benzopyrano[5,4,3-cde][1]benzopyran-5,10-dione

Silymarin: Silybinin + silydianin + silychristin

In vitro tests used for investigating the neuronal Ca uptake inhibitory effect

The Ca uptake was investigated in synaptosomes prepared from rat brain cortex by following the method of P. H. Wu et al. [J. Neurochem. 39, pages 700 to 708 (1982)].

1. Effect on the synaptosomal K^+-induced ^{45}Ca uptake

Male Hannover-Wistar rats weighing 180 to 200 g each were used for the preparation of synaptosomes. After decapitation of the rats, the whole brains were collected in ice-cold physiological saline, the brain cortex was removed and purified from the white matter. The tissue obtained was homogenized in a 10-fold volume of 0.32 M sucrose solution by using a glass-teflon homogenizer. After centrifuging the homogenate in a Janetzki K-70 device at 1,000 x g at 4 °C for 10 minutes, the super-

natant was separated and further centrifuged in a Hitachi CR-26H device at 12,000 x g at 4 °C for 20 minutes. After suspending the pellets in a 0.32 M sucrose solution, the protein content was determined and adjusted to 20 mg/ml.

The composition of the incubation mixture used for measuring the K^+-stimulated ^{45}Ca uptake was: 112 mM NaCl, 5 mM KCl, 1.3 mM $MgCl_2$, 1.2 mM NaH_2PO_4, 1.2 mM $CaCl_2$, 10 mM glucose and 20 mM TRIS. The incubation mixture was saturated by carbogen (containing 95% of O_2 and 5% of CO_2) up to a pH value of 7.4. The compounds to be tested as well as the synaptosome preparation corresponding to 1 mg of protein were added to the medium. The final volume of the incubation mixture was 1 ml. The samples were pre-incubated at 37 °C for 20 minutes. The Ca uptake was initiated by adding a solution containing 2.8 kBq (75 nCi) of $^{45}CaCl_2$. For investigating the K^+-stimulated ^{45}Ca uptake KCl was used in a concentration of 60 mM; NaCl of the same concentration was added to the control samples.

The incubation lasted for 20 minutes. The reaction was stopped by adding 5 ml of ice-cold stopping solution (120 mM NaCl, 5 mM KCl, 5 mM EGTA, 20 mM TRIS-HCl, pH 7.4). After filtering the samples on a Whatman GF/C filter, the protein remaining on the filter was washed twice with 5 ml of washing solution each (132 mM NaCl, 5 mM KCl, 1.3 mM $MgCl_2$, 1.2 mM $CaCl_2$, 20 mM TRIS-HCl, pH 7.4).

The filters were placed in glass cuvets and then dried at 40 °C for 1 hour. Subsequently, 5 ml of a scintillation cocktail were added into each cuvet and the radioactivity of the samples was measured by using a liquid scintillation spectrophotometer (1219 Rackbeta, LKB Wallace).

2. Effect on the synaptosomal veratrine-stimulated ^{45}Ca uptake

Male Hannover-Wistar rats weighing 180 to 200 g each were used for the preparation of synaptosomes. After decapitation of the rats, the whole brains were collected in ice-cold physiological saline, the brain cortex was removed and purified from the white matter. The tissue obtained was homogenized in a 10-fold volume of ice-cold 0.32 M sucrose solution by using a glass-teflon homogenizer. After centrifuging the homogenate in a Janetzki K-70 device at 1000 x g at 4 °C for 10 minutes, the supernatant was further centrifuged in a Hitachi CR-26H device at 12000 x g at 4 °C for 20 minutes. After suspending the pellets in a 0.32 M sucrose solution, the protein content of the solution was determined and adjusted to 20 mg/ml.

The composition of the incubation mixture used for measuring the veratrine-stimulated ^{45}Ca uptake was: 132 mM NaCl, 5 mM KCl, 1.3 mM $MgCl_2$, 1.2 mM NaH_2PO_4, 1.2 mM $CaCl_2$, 10 mM glucose, 20 mM TRIS. The incubation mixture was saturated by carbogen (containing 95% of O_2 and 5% of CO_2) up to a pH value of 7.4. The compounds to be tested as well as the synaptosome preparation corresponding to 1 mg of protein were added to the medium. The final volume of the incubation mixture was 1 ml. The samples were pre-incubated at 37 °C for 20 minutes. The Ca uptake was initiated by adding a solution containing 2.8 kBq (75 nCi) of $^{45}CaCl_2$. For investigating the veratrine-stimulated ^{45}Ca uptake, veratrine was used in a concentration of 20 μM.

The incubation lasted for 20 minutes. The reaction was stopped by adding 5 ml of ice-cold stopping solution (120 mM NaCl, 5 mM KCl, 5 mM EGTA, 20 mM TRIS-HCl, pH 7.4). After filtering the samples on a Whatman GF/C filter, the protein remaining on the filter was washed

twice with 5 ml of washing solution each (132 mM NaCl, 5 mM KCl, 1.3 mM $MgCl_2$, 1.2 mM $CaCl_2$ and 20 mM TRIS-HCl, pH 7.4).

The filters were placed into glass cuvets and then dried at 40 °C for 1 hour. Subsequently, 5 ml of a scintillation cocktail was added into the cuvet each and the radioactivity of the samples was measured by using a liquid scintillation spectrophotometer (1219 Rackbeta, LKB Wallace).

The IC_{50} values were determined on the basis of concentration/effect correlations of the tested compounds and are summarized in Table II.

Table II

Compound No.	Example No.	K^+-stimulated ^{45}Ca uptake	Veratrine-induced ^{45}Ca uptake
0108651	3	27.0 (3)	4.1 (2)
0108536	2	5.4 (2)	2.6 (2)
0108487	2	15.3 (3)	1.9 (2)
0108534	3	33.0 (2)	1.7 (2)
0108489	2	13.2 (3)	2.7 (2)
0107966	1	24.0 (2)	1.1 (3)
0108048	1	30.5 (2)	2.3 (3)
Sabeluzol		13.6 (2)	0.7 (2)
Nimodipine		208.0 (2)	6.7 (3)
Flunarizine		22.6 (2)	1.3 (3)

Number of measurement are given in parentheses.

For the investigation of K^+-induced ^{45}Ca uptake, the membrane depolatization is established by increasing the potassium ion concentration of the extracellular space.

This leads to the opening of the potential-dependent Ca channels. The influx of Ca ions to the cell proceeds through these channels.

For the investigation of veratrine-induced ^{45}Ca uptake, the membrane depolarization is established by increasing the sodium ion concentration of the intracellular space since veratrine impedes the inactivation of Na channels. The thus induced membrane depolarization similarly results in the opening of the Ca channels.

The Ca-antagonistic effect of the compounds was characterized by the IC_{50} values. The cerebroprotective nimopidine, flunarizine and sabeluzol were used as reference substances.

It can be seen from data of Table II that each of the compounds prepared (as described hereinafter in various Examples) possessed a Ca uptake inhibitory effect.

The compounds shown in Table II inhibited the K^+--induced ^{45}Ca uptake to a much higher degree than nimopidine. The compounds Nos. 0108536, 0108489 and 0108487 proved to be particularly effective. When investigating the K^+-stimulated ^{45}Ca uptake, the Ca uptake inhibitory effect of these compounds surpasses even the Ca-antagonistic effect of flunarizine, too. The compound No. 0108536 inhibited the K^+-induced ^{45}Ca uptake twice as effectively as the cerebroprotective salubezol found to be most effective of the reference compounds.

Our studies carried out by using this test indicated that likely, the compounds of the invention inhibited the function of potential-dependent Ca channels.

When investigating the veratrine-induced ^{45}Ca uptake, the activity of each compound according to the invention showed a higher activity in comparison to nimopidine. The veratrine-induced ^{45}Ca uptake inhibitory effect of compounds Nos. 0108487 and 0108534 approximated whereas that of the compound No. 0107966 exceeded the activity of

flunarizine.

Based on study of the veratrine-induced ^{45}Ca uptake it can also be assumed that the compounds according to the invention might be capable to influence the functioning of Na channels, too.

Abbreviations:

EGTA: Ethylene glycol bis(2-aminoethyl) ether N,N'-tetraacetic acid

TRIS: Tris(hydroxymethyl)aminomethane

Nimodipine: 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-methoxyethyl 1-methylethyl ester

Flunarizine: 1-[bis(4-fluorophenyl)methyl]-4-(3-phenyl--2-propenyl)piperazine

Sabeluzol: N-Methyl-N-{1-[3-(4-fluorophenoxy)-2-hydroxypropyl]piperidin-4-yl}-benzothiazole-2-amine

The pharmacological effect of the compounds found to be effective in the in vitro biochemical test were supported by in vivo measurements.

The effects of the compounds were tested on male CFLP/LATI mice weighing 18 to 22 g each. The compounds to be tested were orally administered in a 5% Tween 80 suspension in a volume of 10 ml/kg of body weight. Nimopidine and flunarizine were used as reference substances. The control groups were treated with distilled water containing 5% of Tween 80.

The cytotoxic hypoxia (KCN) test

1 hour after the oral administration of the substances to be tested, the animals were intravenously (i.v.) treated with 5 mg/kg of potassium cyanide (KCN). The time of survival was measured from the administration of potassium cyanide up to the last respiratory movement.

Animals having a survival time longer by 30% than the average survival time of the placebo-treated control group were considered to be protected.

The ED_{50} values (i.e. the dose being effective in 50% of the animals) were calculated from the percentage of the surviving animals by using the probit analysis.

Metrazole convulsion

After a 1-hour pretreatment the animals were subcutaneously (s.c.) treated with a 125 mg/kg dose of pentylenetetrazole (metrazole). The abolishment of tonic extensor convulsions and the survival were considered to be a protective effect.

The ED_{50} values were calculated from the percentage of protected animals by using probit analysis.

The results are summarized in Table III.

Table III

Compound No.	Example No.	ED_{50} mg/kg p.o.	
		KCN	Metrazole
0107966	1	49.3	18.4
0108048	1	47.3	21.2
0108487	2	45.7	8.2
0108489	2	33.9	5.2
0108534	3	49.2	15.5
0108535	3	19.6	22.0
0108536	2	18.7	7.9
0108651	3	50.0	17.4
Flunarizine		58.3	12.3
Nimodipine		85.3	47.0

The antioxidant and Ca^{2+} uptake inhibitory effects of the substances measured under in vitro conditions were

assayed by two pharmacological methods under in vivo conditions.

The cerebroprotective effect was supported by the KCN--lethality inhibitory effect; whereas the Ca^{2+} uptake inhibitory effect was proven by the inhibitory effect on the metrazole convulsion.

By blocking the cytochrome C oxidase, KCN interferes with the metabolism of the cell and therefore results in a lactic acid acidosis and cytotoxic hypoxia; simultaneously, a large amount of Ca^{2+} ions flow into the cell.

In the cytotoxic hypoxia, the compounds Nos. 0108535 and 0108536 were 3 to 4.5 times as active, the compound No. 0108489 was 1.7 to 2.5 times as effective as the reference substances. The effects of other compounds according to the invention were also more favourable in this test.

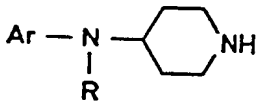
Concerning the protection against convulsions, the anticonvulsive effect of the compounds Nos. 0108487, 0108489 and 0108536 was 1.5 to 2.4 times as pronounced as that of flunarizine, which latter is 4 times as active anticonvulsant as nimodipine. The anticonvulsive effect of other compounds was comparable to that of flunarizine and was approximately 2.0 to 2.5 times as strong as that of nimodipine. Compounds found to have a significant effect both in the antioxidant and Ca uptake inhibitory in vitro tests, were effective in the anticonvulsive test, too.

The compounds according to the invention may be useful for the protection from or treatment of the sequels of Ca--mediated injuries induced e.g. by ischemia, hypoxia or reperfusion. In addition, the compounds tested may be utilized for the treatment of clinical syndromes, where the free radicals play the role of aetiological factors, e.g. cerebral and spinal trauma, apoplexy, stroke, ischemic injuries of cerebrovascular origin, hypoxia

following atherosclerosis as well as in various degenerative neurological diseases such as e.g. Alzheimer's disease or Parkinson's disease.

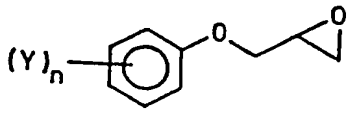
In the above clinical syndromes the expected therapeutical doses of the compounds of the invention are between 0.1 and 40 mg/kg of body weight, which are administered daily once or in several divided doses in oral or parenteral route.

According to the invention the novel aminopropanol derivatives of formula (I) as well as their acid addition salts can be prepared by reacting a 4-aminopiperidine derivative of formula



(II)

wherein R and Ar are as defined above, with a racemic or optically active epoxide derivative of formula



(III)

wherein Y and n are as defined above and, if desired, resolving the so-obtained compound of formula (I) and/or, if desired, converting it to an acid addition salt.

Hereinafter, the preparation of the novel compounds of formula (I) according to the invention will be described in detail.

In the process of the invention an aminopiperidine

derivative of formula (II) is reacted with up to 20% excess of a racemic or optically active epoxide derivative of formula (III) in a protic or aprotic solvent, e.g. alcohols or ether-type solvents, halogenated or aromatic hydrocarbons, such as toluene or xylene, at the boiling point of the solvent used. The reaction time is about 10 hours. In a preferable case the compounds of formula (I) obtained are precipitated from the reaction mixture by cooling or they can be separated after evaporation. Some derivatives may need a purification by column chromatography. By using optically active epoxides of formula (III), the compounds of formula (I) obtained will of course be optically active. By reacting racemic compounds of formula (III), the compounds of formula (I) obtained will be in racemic form which, if desired, can be separated to the pure enantiomers by using resolution methods known per se.

Of the 4-aminopiperidine derivatives of formula (II) used as starting substances, e.g. N-methyl-N-(3-methylphenyl)-4-aminopiperidine (see European patent specification No. 156,433), N-phenyl-4-aminopiperidine [Chem. Pharm. Bull. 33, (5) pages 1826 to 1835 (1985)], N-(2,6-dimethylphenyl)-4-aminopiperidine (United States patent specification No. 4,126,689), N-(4-methoxyphenyl)-4-aminopiperidine, N-(4-chlorophenyl)-4-aminopiperidine and N-(4-fluorophenyl)-4-aminopiperidine (United States patent specification No. 3,686,187) are known. Other derivatives required can be prepared according to the methods described in the above literature references.

Of the 4-naphthylaminopiperidine derivatives of formula (II) e.g. 4-(1-naphtyl)-aminopiperidine is described in Swiss patent specification No. 535,767. Other derivatives desired can be prepared by using the methods described therein.

The epoxide derivatives of formula (III) are known

compounds, a number of which are commercially available. Optically active substances of formula (III) can be prepared by following, e.g. the methods published in: J. Org. Chem. 54, pages 1298 to 1304 (1989).

If desired, the racemic or optically active compounds of formula (I) may be converted to their acid addition salts in a known manner.

The salt formation may be carried out in an inert organic solvent, e.g. by dissolving the compound of formula (I) in the selected solvent and then portionwise adding the appropriate acid to this solution until the pH value of the mixture becomes strongly acidic (pH value of about 1). However, the salts may also be formed by adding a calculated amount of the desired acid dissolved in the solvent of choice to the above solution. Thereafter, the acid addition salt precipitated is separated from the reaction mixture in a suitable manner, e.g. by filtration.

The active agents of formula (I) can be formulated in pharmaceutical compositions by mixing them with non-toxic, inert, solid or liquid carriers and/or auxiliaries commonly used in the therapy for parenteral or enteral administration. Useful carriers are e.g. water, gelatine, lactose, starch, pectin, magnesium stearate, stearic acid, talc, vegetable oils, such as peanut oil, olive oil and the like. The active agents can be formulated in any usual pharmaceutical composition, particularly solid composition, e.g. rounded or edged tablet, dragée or capsule such as gelatine capsule, pill, suppository and the like. Optionally, these compositions may contain also other commonly used pharmaceutical auxiliaries, e.g. stabilizers, preservatives, wetting agents, surfactants, emulsifying agents and the like. The compositions can be prepared in a known manner, e.g. by sieving, mixing, granulating and compressing the components in the case of solid compositions. The compositions may be subjected to

other usual operations of the pharmaceutical technology, e.g. sterilization.

The invention also relates to a method for inhibiting lipid peroxidation as well as treating the sequels thereof furthermore, for the protection from or treatment of the sequels of Ca-mediated injuries. This method comprises administering a therapeutically effective amount of an active agent of the formula (I) or a pharmaceutically acceptable acid addition salt thereof to the patient.

The invention is illustrated in detail by the aid of the following non-limiting Examples.

Example 1

Preparation of (±)-1-phenoxy-3-{4-[(1-naphthyl)amino]-piperidin-1-yl}-2-propanol [(I), Ar = 1-naphthyl, R = H, Y = H; compound No. 0107966]

After suspending 11.7 g (0.030 mol) of 4-[(1-naphthyl)amino]piperidine dihydrochloride [(II), Ar = 1-naphthyl, R = H] in 240 ml of chloroform, 120 ml of 4 N aqueous sodium hydroxide solution are added to the above suspension and the mixture is then stirred until dissolution of the solid material. After separating the two phases the aqueous layer is extracted with 30 ml of chloroform and the combined organic phase is washed with 30 ml of water. The chloroform solution is dried and evaporated under reduced pressure. The oily residue is dissolved in 120 ml of xylene, 6.1 ml (0.045 mol) of (±)-1-phenoxy-2,3-epoxypropane [(III), Y = H] are added to the solution, then the reaction mixture is boiled under reflux for 10 hours while stirring. After cooling the product precipitated from the solution is filtered and recrystallized from 200 ml of acetonitrile to give the title compound in a yield of 9.0 g (85.5%), m.p.: 160-162 °C.

By following the above process, the (±) derivatives of formula (I) listed hereinafter were prepared by reacting

the corresponding piperidine derivatives of formula (II) with the suitably substituted epoxy compounds of formula (III).

Ar	R	Y	M.p. (°C)	Solvent of crystallization	Compound No.
1-naphthyl	H	3,4-$(CH=CH)_2$	161-163	ethyl acetate	0108199
1-naphthyl	H	4-Br	162-165	ethyl acetate	0108958
1-naphthyl	CH_3	H	127-128	xylene	0109402
1-naphthyl	H	C_6H_5	162-164	xylene	0109574
4-Cl-phenyl	H	H	119-120	ethanol	0108048
4-Cl-phenyl	H	3,4-$(CH=CH)_2$	163-165	toluene	0108200
4-Cl-phenyl	H	4-Br	145-150	methanol	0108859
4-F-phenyl	H	H	120-122	xylene	0108943
4-F-phenyl	H	4-F	126-128	ethanol	0108874
4-F-phenyl	H	4-Cl	136-138	ethanol	0108875
4-NO_2-phenyl	H	H	156-157	ethanol	0108737
4-NO_2-phenyl	H	4-F	153-154	ethanol	0108738
phenyl	H	H	116-117	ethanol	0108648
phenyl	H	4-F	136-138	toluene	0108685
4-CH_3O-phenyl	H	H	118-120	xylene	0109222

Similarly, by using the above method, (±)-1-(4-fluorophenoxy)-3-{4-[(2-naphthyl)amino]piperidin-1-yl}-2-propanol [(I), Ar = 2-naphthyl, R = H, Y = 4-F] [m.p.: 166-168 °C (after recrystallization from ethyl acetate), compound No. 0108650] was prepared from 4-[(2-naphthyl)-amino]piperidine dihydrochloride [(II), Ar = 2-naphthyl, R = H] and (±)-1-(4-fluorophenoxy)-2,3-epoxypropane [(III), Y = 4-F].

Example 2

Preparation of (±)-1-(4-chlorophenoxy)-3-{4-[(1-naphthyl)amino]piperidin-1-yl}-2-propanol [(I), Ar = 1-naphthyl, R = H, Y = 4-Cl; compound No. 0108536]

After adding 200 ml of 4 N aqueous sodium hydroxide solution to a suspension containing 15.0 g (0.050 mol) of 4-[(1-naphthyl)amino]piperidine dihydrochloride [(II), Ar = 1-naphthyl, R = H] in 400 ml of chloroform, the mixture is stirred until dissolution of the solid material. After separating the two phases the aqueous layer is extracted with 50 ml of chloroform, then the combined organic phase is washed with 50 ml of water. The chloroform solution is dried and evaporated under reduced pressure. After dissolving the oily residue in 200 ml of xylene, 10.2 g (0.055 mol) of (±)-1-(4-chlorophenoxy)-2,3-epoxypropane [(III), Y = 4-Cl] are added, then the reaction mixture is boiled under reflux for 10 hours while stirring. After cooling down, the solution is evaporated under reduced pressure and the residue is recrystallized from 100 ml of ethanol to obtain the title compound in a yield of 19.2 g (93.5%), m.p.: 165-167 °C.

Similarly, by using the above process, the (±) derivatives of formula (I) listed hereinafter were prepared by reacting the corresponding piperidine derivatives of formula (II) with the suitably substituted epoxy compounds of formula (III).

Ar	R	Y	M.p. (°C)	Solvent of crystallization	Compound No.
1-naphthyl	H	2,3,4,5,6-penta-F	123-124	methanol	0107968
1-naphthyl	CH_3	4-Cl	100-102	diisopropyl ether	0109403
4-CH_3-phenyl	H	4-F	140-142	ethanol	0108880
4-Cl-phenyl	H	4-F	136-138	ethanol	0108487
4-Cl-phenyl	H	4-Cl	146-148	ethanol	0108489
4-Cl-phenyl	H	2,3,4,5,6-penta-F	100-102	ethanol	0108179
4-Cl-phenyl	H	2,3-(CH=CH)-	139-141	ethanol	0108488
2-Cl-phenyl	H	H	92-94	ether	0108864
2-Cl-phenyl	H	4-F	108-110	ethanol	0108865
2-Cl-phenyl	H	4-Cl	101-103	ethanol	0108866
3-Cl-phenyl	H	H	124-126	ethanol	0108867
3-Cl-phenyl	H	4-F	126-128	ethanol	0108868
3-Cl-phenyl	H	4-Cl	131-133	ethanol	0108869
2,5-di-Cl-phenyl	H	H	107-108	ethanol	0109006
2,5-di-Cl-phenyl	H	4-F	105-106	ethanol	0108947
2,5-di-Cl-phenyl	H	4-Cl	119-121	ether	0108948
4-Br-phenyl	H	H	103-104	ethanol	0108876
4-Br-phenyl	H	4-F	123-125	ethanol	0108877
4-Br-phenyl	H	4-Cl	143-145	ethanol	0108878
4-CH_3-phenyl	H	H	121-123	ethanol	0108879
4-CH_3-phenyl	H	4-Cl	126-128	ether	0109001
4-CH_3O-phenyl	H	4-Cl	141-143	ethanol	0109223
4-CH_3-phenyl	CH_3	H	72-73	diisopropyl ether	0109326
4-Cl-phenyl	CH_3	4-C_6H_5	135-136	methanol	0109537

Similarly, by using the above method, (±)-1-(3-phenoxy)-3-{4-[(2-naphthyl)amino]piperidin-1-yl}-2-propanol [(I), Ar = 2-naphthyl, R = H, Y = H; compound No. 0508649] was prepared from 4-[(2-naphthyl)amino]piperidine dihydrochloride [(II), Ar = 2-naphthyl, R = H] and (±)-1-phenoxy-2,3-epoxypropane. [(III), Y = H]. The melting point of the compound obtained is 156-157 °C (after recrystallization from ethanol).

Example 3

Preparation of (±)-1-(1-naphthyloxy)-3-{4-[(1-naphthyl)amino]piperidin-1-yl}-2-propanol [(I), Ar = 1-naphthyl, R = H, Y = 2,3-(CH=CH)$_2$-); compound No. 0108535]

After adding 40 ml of 4 N aqueous sodium hydroxide solution to a suspension containing 3.9 g (0.010 mol) of 4-[(1-naphthyl)amino]piperidine dihydrobromide [(II), Ar = 1-naphthyl, R = H] in 80 ml of chloroform, the mixture is stirred until dissolution of the solid material. After separating the two phases, the aqueous layer is extracted with 10 ml of chloroform, then the combined organic phase is washed twice with 10 ml of water each. The chloroform solution is dried and evaporated under reduced pressure. The oily residue is dissolved in 40 ml of toluene, and after adding 2.2 g (0.011 mol) of (±)-1-(1-naphtyloxy)-2,3-epoxypropane [(III), Y = 2,3-(CH=CH)$_2$-] to the above solution, the reaction mixture is boiled under reflux for 10 hours while stirring. After evaporating the solution under reduced pressure, the residue is purified by chromatography on a silica gel column (particle size 0.063-0.200 mm) by using a 9:1 mixture of chloroform and methanol as eluent. The fractions containing the pure product are evaporated and the residue is recrystallized from 30 ml of ethanol to give the title product in a yield of 1.8 g (42%), m.p.: 111-113 °C.

By following the above process the (±) derivatives of formula (I) listed hereinafter were prepared by reacting the corresponding 4-aminopiperidine derivatives of formula (II) with the suitably substituted epoxy compounds of formula (III).

Ar	R	Y	M.p. (°C)	Solvent of crystallization	Compound No.
1-naphthyl	H	4-F	168-170	ethyl acetate	0108534
1-naphthyl	H	2-CH_3O	111-113	isopropanol	0108651
1-naphthyl	H	3-CH_3	131-133	ethanol	0108652
4-Cl-phenyl	H	2-CH_3O	102-103	ethanol	0108653
4-Cl-phenyl	H	3-CH_3	129-130	ethanol	0108654
4-Br-phenyl	CH_3	H	97-98	petroleum ether	0109327

Example 4

Preparation of (±)-1-(4-fluorophenoxy)-3-{4-[(2,6-dimethylphenyl)amino]piperidin-1-yl}-2-propanol dihydrochloride [(I), Ar = 2,6-di-CH_3-phenyl, R = H, Y = 4-F; compound No. 0108945]

By following the procedure described in Example 1, 3.70 g (0.010 mol) of 4-[(2,6-dimethylphenyl)amino]-piperidine dihydrobromide [(II), Ar = 2,6-dimethylphenyl, R = H] are converted to the free base form. After dissolving the evaporation residue in 40 ml of xylene and adding 1.85 g (0.011 mol) of (±)-1-(4-fluorophenoxy)-2,3-epoxypropane [(III), Y = 4-F], the reaction mixture is boiled under reflux for 10 hours while stirring. After cooling down, the solution is evaporated under reduced pressure and the residue is purified by chromatography on a silica gel column (particle size 0.063-0.200 mm). A 95:5 mixture of chloroform and methanol is used as eluent. After eva-

porating the fractions containing the pure product, the oily residue is dissolved in 20 ml of ether and an ethyl acetate solution containing hydrogen chloride is dropwise added to the solution until achieving a pH value of 1. The precipitate is filtered and dried on air to obtain the title porduct in a yield of 3.3 g (74%), m.p.: 241-242 °C.

By following the above process the hydrochlorides of the (±) derivatives of formula (I) listed hereinafter were prepared by reacting the corresponding starting substances of formula (II) and formula (III).

Ar	R	Y	M.p. (°C)	Solvent of crystallization	Compound No.
1-naphthyl	H	H	250-252		
2,6-dimethyl-phenyl	H	H	186-188		0108944
2,6-dimethyl-phenyl	H	4-Cl	111-113		0108946
4-Cl-phenyl	CH_3	4-Cl	216-218	isopropanol	0109170

Example 5

Preparation of (+)-1-phenoxy-3-{4-[(1-naphthyl)amino]-piperidin-1-yl}-2-propanol [(I), Ar = 1-naphthyl, R = H, Y = H;]

After adding 40 ml of 4 N aqueous sodium hydroxide solution to a suspension containing 3.0 g (0.010 mol) of 4-[(1-naphthyl)amino]piperidine dihydrochloride [(II), Ar = 1-naphthyl, R = H] in 80 ml of chloroform, the mixture is stirred until the dissolution of the solid material. After separating the two phases, the aqueous layer is extracted with 10 ml of chloroform, then the combined organic phase is washed twice with 10 ml of water each. The chloroform solution is dried then evaporated under reduced pressure. After dissolving the oily residue

in 40 ml of xylene and adding 1.65 g (0.011 mol) of (+)-1-phenoxy-2,3-epoxypropane [(III), Y = H], the reaction mixture is boiled under reflux for 10 hours while stirring. After cooling the solution. the precipitate is filtered and recrystallized from 20 ml of ethyl acetate to obtain the title product in a yield of 1.63 g (43%), m.p.: 153-155 °C., $[\alpha]_D^{25}$ = +5.8° (c = 1, dimethylformamide).

(-)-1-Phenoxy-3-{4-[(1-naphthyl)amino]piperidin-1-yl}-2-propanol [(I), Ar = 1-naphthyl, R = H, Y = H], [m.p.: 162-164 °C (after recrystallization from ethyl acetate), $[\alpha]_D^{25}$ = -4.8° (c = 1, dimethylformamide)] was prepared by following the above method and using 4-[(1-naphthyl)-amino]piperidine dihydrochloride [(II), Ar = 1-naphthyl, R = H] and (-)-1-phenoxy-2,3-epoxypropane [(III), Y = H] as starting substances.

Example 6

Preparation of (-)-1-phenoxy-3-[4-{[N-(1-naphthyl)--N-methyl]amino}piperidin-1-yl]-2-propanol [(I), Ar = 1-naphthyl, R = CH_3, Y = H]

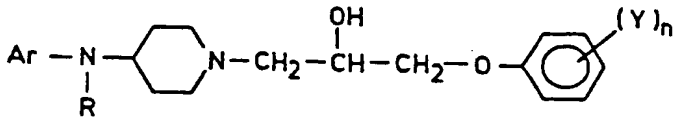
After liberating the base from 3.2 g (0.010 mol) of 4-{[N-methyl-N-(1-naphthyl)]amino}piperidine dihydrochloride [(II), Ar = 1-naphthyl, R = CH_3] as described in Example 5, the oily residue is dissolved in 40 ml of xylene and, after adding 1.65 g (0.011 mol) of (-)-1-phenoxy-2,3-epoxypropane [(III), Y = H], the reaction mixture is boiled under reflux for 10 hours while stirring. After evaporation of the solution under reduced pressure, the residue is purified by chromatography on a silica gel column (particle size 0.063-0.200 mm). Acetone is used as eluent. After evaporating the fractions containing the pure product, the residue is recrystallized from 20 ml of ethanol to give the title product in a yield of 0.82 g (21%), m.p.: 115-117 °C, $[\alpha]_D^{25}$ = -10.8° (c = 1, dimethylformamide).

By using the above process (+)-1-phenoxy-3-[4-{[N-(1-

-naphthyl)-N-methyl]amino}piperidin-1-yl]-2-propanol was prepared from 4-{[N-methyl-N-(1-naphthyl)]amino}piperidine dihydrochloride [(II), Ar = 1-naphthyl, R = CH_3] and (+)-1-phenoxy-2,3-epoxypropane [(III), Y = H]. The melting point of the compound obtained is 120-122 °C, $[\alpha]_D^{25}$ = +10.9° (c = 1, dimethylformamide).

C l a i m s

1. Aminopropanol derivatives of the formula



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

n is an integer of 0, 1, 2, 3, 4 or 5

in racemic or optically active form, as well as acid addition salts thereof.

2. A compound as claimed in claims 1 which is selected from the group consisting of

1-(4-chlorophenoxy)-3-{4-[(1-naphthyl)amino]piperidin-1-yl}-2-propanol,

1-(1-naphthyloxy)-3-{4-[(1-naphthyl)amino]piperidin-1-yl}-2-propanol,

1-(4-fluorophenoxy)-3-{4-[(1-naphthyl)amino]piperidin-1-y}-2-propanol,

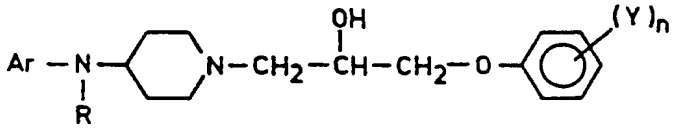
1-(4-fluorophenoxy)-3-{4-[(4-chlorophenyl)amino]piperidin-1--yl}-2-propanol,

1-(4-chlorophenoxy)-3-{4-[(4-chlorophenyl)amino]piperidin-1--yl}-2-propanol,

in racemic or optically active form as well as acid addition salts of these compounds.

3. A pharmaceutical composition, w h i c h

c o m p r i s e s as active ingredient a racemic or optically active aminopropanol derivative of formula



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

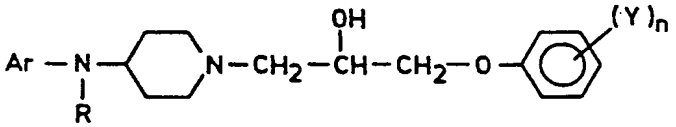
Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

n is an integer of 0, 1, 2, 3, 4 or 5

or a pharmaceutically acceptable acid addition salt thereof in admixture with a carrier and/or other additive commonly used in the pharmaceutical industry.

4. A process for the preparation of the novel aminopropanol derivatives of formula



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

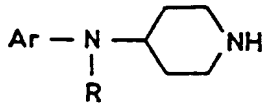
Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl,

2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

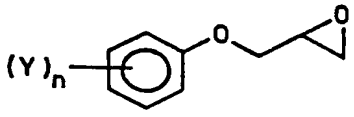
n is an integer 0, 1, 2, 3, 4 or 5

in racemic or optically active form and acid addition salts of these compounds, which comprises reacting a 4-aminopiperidine derivative of formula



(II)

wherein R and Ar are as defined above, with a racemic or optically active epoxide derivative of formula



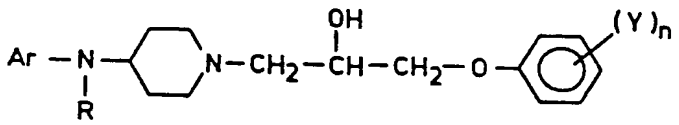
(III)

wherein Y and n are as defined above and, if desired, resolving the so-obtained compound of formula (I) and/or, if desired, converting it to an acid addition salt.

5. A process as claimed in claim 4, which comprises reacting the 4-aminopiperidine derivative of formula (II) with an excess of the epoxide derivative of formula (III).

6. A process as claimed in claim 4, which comprises carrying out the reaction of the compound of formula (II) with the compound of formula (III) in an organic protic or aprotic solvent, at the boiling point of the solvent used.

7. A process for the preparation of a pharmaceutical composition, which comprises mixing as active ingredient a novel racemic or optically active aminopropanol derivative of formul



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

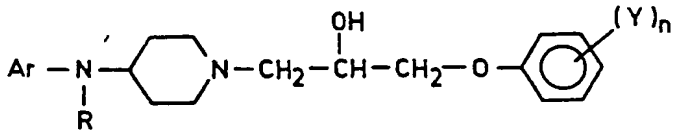
Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

n is an integer of 0, 1, 2, 3, 4 or 5

or a pharmaceutically acceptable acid addition salt thereof with a carrier and/or other additive commonly used in the pharmaceutical industry and converting the mixture to a pharmaceutical composition.

8. Method for inhibiting lipid peroxidation and treating the sequels thereof as well as for protection from or treatment of the sequels of calcium-medicated injuries induced e.g. by ischemia, hypoxia or reperfusion and for treating various degenerative neurological diseases such as e.g. Alzheimer's disease or Parkinson's disease which comprises administering to a patient to be treated a therapeutically effective amount of an optically active or racemic aminopropanol derivative of formula



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

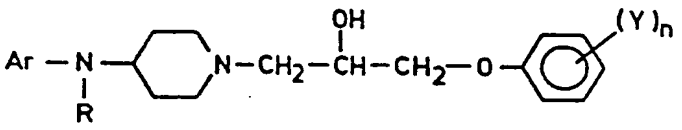
Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

n is an integer of 0, 1, 2, 3, 4 or 5

or a pharmaceutically acceptable acid addition salt thereof alone or in the form of a pharmaceutical composition.

9. The use of a compound of formula



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

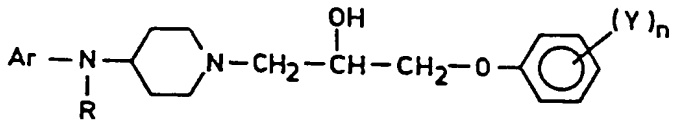
Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

n is an integer of 0, 1, 2, 3, 4 or 5

or a pharmaceutically acceptable acid addition salt

thereof for the preparation of a pharmaceutical composition for inhibiting lipid peroxidation and treating the sequels thereof as well as for protection from or treatment of the sequels of calcium-medicated injuries induced e.g. by ischemia, hypoxia or reperfusion and for treating various degenerative neurological diseases such as e.g. Alzheimer's disease or Parkinson's disease.

10. The use of a compound of formula



(I)

wherein

R means hydrogen or a C_{1-4}alkyl group;

Ar stands for a phenyl group optionally substituted by at most two halogens, C_{1-4}alkyl, C_{1-4}alkoxy or nitro group(s); or a naphthyl group;

Y represents halogen, C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, 2,3-$(CH=CH)_2$- or 3,4-$(CH=CH)_2$- group; and

n is an integer of 0, 1, 2, 3, 4 or 5

or a pharmaceutically acceptable acid addition salt thereof for inhibiting lipid peroxidation and treating the sequels thereof as well as for protection from or treatment of the sequels of calcium-medicated injuries induced e.g. by ischemia, hypoxia or reperfusion and for treating various degenerative neurological diseases such as e.g. Alzheimer's disease or Parkinson's disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 93/00033

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: C 07 D 211/58, A 61 K 31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 07 D, A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB, A, 1 410 783 (JOHN WYETH & BROTHER LTD.) 22 October 1975 (22.10.75), claims 1,13,14,16,17.	1,3-7,9
A	US, A, 3 894 030 (JANSSEN et al.) 08 July 1975 (08.07.75), claim 1.	1
A	US, A, 3 818 017 (JANSSEN et al.) 18 June 1974 (18.06.74), claim 1.	1
A	DE, A1, 2 234 332 (SUMITOMO CHEMICAL CO., LTD) 08 February 1973 (08.02.73), claims 1,3,8,9.	1,3-7,9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 1993 (27.09.93)	20 October 1993 (20.10.93)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Scharf e.h. Telephone No. 1/5337058/29

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 93/00033

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8,10
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 8 and 10 are considered to be methods for threatment of the human or animal body by therapy and are subject matter which the International Searching Authority is not required to search under Article 17(2)(a)(i) and Rule 39(iv).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 93/00033

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB A 1410783	22-10-75	keine - none - rien	
US A 3894030	08-07-75	keine - none - rien	
US A 3818017	18-06-74	keine - none - rien	
DE 2234332		DE A1 2234332	08-02-73
		DE B2 2234332	08-01-76
		DE C3 2234332	19-08-76
		BE A1 786155	03-11-72
		CA A1 977348	04-11-75
		CH A 576466	15-06-76
		DE A1 2265034	20-11-75
		FR A1 2145640	23-02-73
		FR B1 2145640	31-10-75
		GB A 1368012	25-09-74
		JP B4 55011670	26-03-80
		NL A 7209646	16-01-73
		SE B 393380	09-05-77
		SE C 393380	18-08-77
		US A 4080328	21-03-78